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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,421	01/27/2004	Masatake Kudoh	14879-090002	4485

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,421	KUDOH ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16,18,21 and 25-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-16, 18, 21 and 25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/978,758.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/978,758, now issued as U.S. Patent No. 6,706,507, which is a CIP of PCT/JP01/01082.

The amendment filed on October 4, 2005, amending claims 15, 16, 18, 21, canceling claims 17, 19-20 and 23-24 and adding claims 25-38, has been entered.

Claims 15-16, 18, 21 and 25-38 are pending and are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 and 30 and claims 16, 18, 21, 25-29 and 31-38 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 30 recite the phrase "hybridizes under stringent conditions". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner as to what hybridization conditions are encompassed in the phrase (i.e. low stringency, high stringency, etc.). A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. Therefore, it is unclear from the specification or from the claim as to what hybridization conditions are encompassed in the claims. Examiner requests clarification of the above phrase.

Claims 15 and 37-38 and claims 16, 18, 21, 25-36 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 37-38 recite the phrase "polypeptide comprising the amino acid sequence of SEQ ID NO:2 with up to 50/10 conservative amino acid substitutions". The metes and bounds of this phrase in the context of the above claims are not clear to the Examiner. It is not clear to the Examiner if the "polypeptide" is a variant of SEQ ID NO:2 or if the "polypeptide" has the amino acid sequence of SEQ ID NO:2. If the latter is true, since the polypeptide must have the amino acid sequence of SEQ ID NO:2, said polypeptide can not have any amino acid substitutions. Examiner requests clarification of the above phrase.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 recites the phrase "substantially pure". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner what is considered as "substantially pure" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition, those skilled in the art would be unable to conclude if a dehydrogenase is

"substantially pure" without knowing the metes and bounds of the phrase. Examiner requests clarification of the above phrase.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 recites the phrase "chemically treated". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner what is considered as "chemically treated" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition, those skilled in the art would be unable to conclude if a dehydrogenase is "chemically treated" without knowing the metes and bounds of the phrase and whether such chemically treated enzyme continues to have the same activity. Examiner requests clarification of the above phrase.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-16, 18, 21, 25-34 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the producing a (S)-4-halo-3-hydroxybutyric acid ester derivative using a (R)-2-octanol

dehydrogenase having the amino acid sequence SEQ ID NO:2 or a transformant producing said enzyme, does not reasonably provide enablement for a method for the production of (S)-4-halo-3-hydroxybutyric acid ester derivatives using a (R)-2-octanol dehydrogenase having 70-95% sequence identity to SEQ ID NO:2 or a (R)-2-octanol dehydrogenase encoded by a polynucleotide that hybridizes to SEQ ID NO:2 under any hybridization conditions or a transformant producing said enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 15-16, 18, 21, 25-34 and 37 are drawn to a method for the producing (S)-4-halo-3-hydroxybutyric acid ester derivatives using a (R)-2-octanol dehydrogenase having 70-95% sequence identity to SEQ ID NO:2 or a (R)-2-octanol dehydrogenase encoded by a polynucleotide that hybridizes to SEQ ID NO:2 under any "stringent hybridization" conditions or a transformant producing said enzyme. The claims encompass a method for producing (S)-4-halo-3-hydroxybutyric acid ester derivatives by using any or all recombinants, variants and mutants of SEQ ID NO:2 having up to

30% amino acid modifications of SEQ ID NO:2 or any or all recombinants, variants and mutants of SEQ ID NO:2 encoded by a polynucleotide that hybridizes to SEQ ID NO:2 under any hybridization conditions. Therefore, the claims are drawn to a method of producing (S)-4-halo-3-hydroxybutyric acid ester derivatives using variants, mutant and recombinants of SEQ ID NO:2 having any structure. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of (R)-2-octanol dehydrogenase variants and mutants and substrates, broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method of producing a (S)-4-halo-3-hydroxybutyric acid ester derivatives using the (R)-2-octanol dehydrogenase of SEQ ID NO:2 or a host cell producing said enzyme. It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of SEQ ID NO:2. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptide, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue

experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method for the production of (S)-4-halo-3-hydroxybutyric acid ester derivatives using any or all mutants and variants of SEQ ID NO:2, because the specification does not establish: (A) regions of the (R)-2-octanol dehydrogenase structure which may be modified without affecting (R)-2-octanol dehydrogenase activity; (B) the general tolerance of (R)-2-octanol dehydrogenase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including a method for the production of (S)-4-halo-3-hydroxybutyric acid ester derivatives using a (R)-2-octanol dehydrogenase having 70-95% sequence identity to SEQ ID NO:2 or a (R)-2-octanol dehydrogenase encoded by a polynucleotide that hybridizes to SEQ ID NO:2 under any hybridization conditions. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of which variants (R)-2-octanol dehydrogenase to use to produce (S)-4-halo-3-hydroxybutyric acid ester derivatives is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that since the claims have been amended to more particularly define the structural and/or physiochemical features of the (R)-2-octanol dehydrogenase and that none of the pending claims encompass a method of using any (R)-2-octanol dehydrogenase, the claims are enabled. Examiner respectfully disagrees. In light of the amendment of the claims, Examiner has amended the rejection. The claims encompass a method for producing (S)-4-halo-3-hydroxybutyric acid ester derivatives by using any or all recombinants, variants and mutants of SEQ ID NO:2 having up to 30% amino acid modifications of SEQ ID NO:2 or any or all recombinants, variants and mutants of SEQ ID NO:2 encoded by a polynucleotide that hybridizes to SEQ ID NO:2 under any hybridization conditions. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the

desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation in order to arrive at polypeptides having 70-95% amino acid sequence identity to SEQ ID NO:2 and use them to produce (S)-4-halo-3-hydroxybutyric acid ester derivatives . While the art may teach in general, the structure of the dehydrogenase, conserved amino acid sequences, and etc, such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art to make the claimed polypeptides. Hence the rejection is maintained.

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Patent Examiner 1652